Mammary Stem Cell Self-Renewal Is Regulated by Slit2/Robo1 Signaling through SNAI1 and mINSC.

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Public Summary:
Tissue homeostasis depends on the balanced self-renewal of stem cells. Ballard et al. describe a mechanism whereby the extracellular cue SLIT2 signals through receptor ROBO1 to regulate the asymmetric self-renewal of basal stem cells during mammary gland development by controlling Inscuteable expression through the transcription factor Snail.

Scientific Abstract:
Tissue homeostasis requires somatic stem cell maintenance; however, mechanisms regulating this process during organogenesis are not well understood. Here, we identify asymmetrically renewing basal and luminal stem cells in the mammary end bud. We demonstrate that SLIT2/ROBO1 signaling regulates the choice between self-renewing asymmetric cell divisions (ACDs) and expansive symmetric cell divisions (SCDs) by governing Inscuteable (mInsc), a key member of the spindle orientation machinery, through the transcription factor Snail (SNAI1). Loss of SLIT2/ROBO1 signaling increases SNAI1 in the nucleus. Overexpression of SNAI1 increases mInsc expression, an effect that is inhibited by SLIT2 treatment. Increased mInsc does not change cell proliferation in the mammary gland (MG) but instead causes more basal cap cells to divide via SCD, at the expense of ACD, leading to more stem cells and larger outgrowths. Together, our studies provide insight into how the number of mammary stem cells is regulated by the extracellular cue SLIT2.